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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,196	04/13/2001	Barnett S. Pitzele	PHAR 7979/3313US	5348

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EXAMINER	
ZUCKER, PAUL A	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,196	PITZELE ET AL.	
	Examiner	Art Unit	
	Paul A. Zucker	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8-11,16-19 and 24-32* is/are rejected.

7)☒ Claim(s) *4-7,12-15 and 20-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

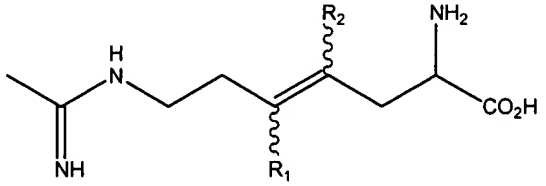
1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Current Status

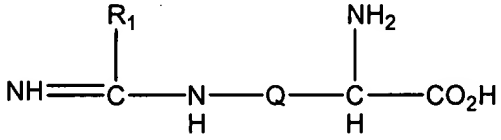
1. This action is responsive to Applicants' amendment of 3 October 2003 in Paper No 14.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Claims 1-32 are pending.
4. Claims 1-3, 8-11, 16-19 and 24-30 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Beams et al (WO 93/13055-A1 07-1993).

Instantly claimed are compounds (geometric and stereoisomers) of Formula (I), where R_1 and R_2 may be H or methyl, or their pharmaceutically acceptable salts :



and pharmaceutical compositions thereof.

Beams teaches (Page 5, line 26-page 7, line 35) a genus of nitric oxide synthase inhibitors of general formula (I):



Where R^1 may be a C_{1-6} straight chain or branched alkyl and Q may be an alkylene, alkenylene or alkynylene group having 3-6 carbons. Beams further teaches (Page 5, line 37-page 6, line 1) optional substitution of Q by one or more C_{1-3} alkyl groups. A

preferred embodiment of the compounds is further taught (Page 6 lines 30-36) where Q = $-(CH_2)_vCH=CH(CH_2)_w-$ where v = 0-3; w = 0 to 3; and v + w = 2-4. The instantly claimed compounds correspond to v =2, w =1 and thus fall within the narrow subgenus suggested by Beams. Beams further teaches (Page 7, lines 1-3) a preferred value for R^1 of methyl. Beams teaches (Page 3, lines 23-34) that the genus encompasses all stereoisomeric forms (both E, Z and R,S).

Beams teaches (Page 8, line 14 – page 11, line 4) pharmaceutical compositions of the compounds as well.

Instant claim 28, in particular, (1^{st} and 2^{nd} listed compounds) is obvious over Beams' exemplification (Page 13, lines 23-31, Example 3, and page 15, lines 1-10, Example 8) of (±)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride. The 1^{st} and 2^{nd} listed compounds of claim 28 are simply the salts of the adjacent higher homologue with one additional chain methylene unit between the double bond and the amidino group. One of ordinary skill in the art would have had an expectation of similar properties for the instant compounds and those of Beams since they are adjacent homologues. The instantly claimed compounds are therefore *prima facie* obvious over the compounds of Beams.

Thus the instantly claimed compounds and the pharmaceutical compositions containing them would have been obvious to one of ordinary skill in the art. The motivation for the instantly claimed invention would have been to develop other

compounds in the genus taught by Beams and apply them, in the compositions taught by Beams, to the methods taught by Beams. The expectation for success would have been near certitude since Beams' genus completely embraces the instant compounds which, Beams' teaches, have the instantly desired activity as nitric oxide synthase inhibitors.

Examiner's Response to Applicants' Remarks with Regard to This Rejection

5. Applicants have presented arguments with regard to this rejection. The Examiner responds to these below:

    a. Applicants argue that, viewed as a whole, WO 93/13055 does not teach or suggest the instant invention. The Examiner disagrees. The instantly claimed compounds represent the simplest members of the genus of compounds described by Beams. Beams further, as set forth in the rejection above, provides sufficient guidance for one of ordinary skill in the art to the make the selection of variable groups required to produce the instantly claimed compounds. In fact, as Applicants admit, the heptenoic acids exemplified by Beams are adjacent homologues. This taken into consideration with the fact that the compounds of Beams' genus are taught to have the instantly desired utility makes the instant invention, viewed as a whole, obvious over the teachings of Beams.

    b. Applicants argue that compounds in which R^1 and R^2 are other than H are more remote than the compounds of Beams. The Examiner agrees and has

modified the rejection set forth above to exclude where R^1 and R^2 are other than H.

c. Applicants further argue that publications by Lee and Young teach that imposing conformational rigidity is not a favorable approach for improving NOS inhibitor selectivity. To this the Examiner responds with two points:

   i. The structures of the compounds of Lee (whose study Young refers to) either contain aromatic rings on the backbone and or are pentenoic acids and would therefore be much more rigid overall than the hexenoic acids of Beams or the instant heptenoic acids. The compounds of Lee are more remote from the instantly claimed compounds than are the compounds containing a double bond exemplified by Beams.

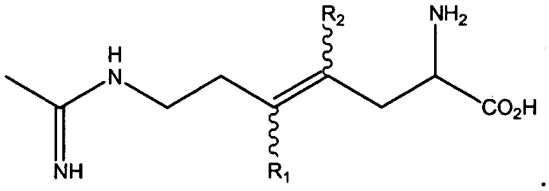
   ii. Beams (which predates Lee) teaches that placing a double bond along the backbone chain produces compounds having the instantly desired activity/selectivity.

d. Finally the Examiner does not understand how Applicants' conclusion that the Young reference teaches away from the present invention naturally flows from the fact that two of the authors of this reference are also inventors on WO 93-13055. The compounds of Young are, as in the case of Lee, more remote from the present compounds than are the compounds of Beams (who exemplifies adjacent homologues).

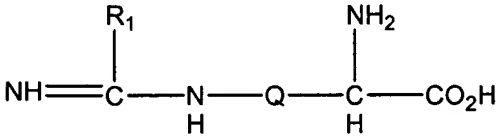
Applicant's arguments filed 3 October 2003 have been fully considered but they are not persuasive for the reasons set forth above.

6. Claims 31 and 32 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Beams et al (WO 93/13055-A1 07-1993).

Instantly claimed are methods for selectively inhibiting the inducible isoform of Nitric Oxide Synthase employing the compounds (geometric and stereoisomers) of Formula (I), where R_1 and R_2 may be H or methyl, or their pharmaceutically acceptable salts :



Beams teaches (Page 5, line 26-page 7, line 35) a genus of nitric oxide synthase inhibitors of general formula (I):



Where the variable groups are as defined at the above-noted location. In particular, Beams' exemplifies (Page 13, lines 23-31, Example 3, and page 15, lines 1-10, Example 8) of (±)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride. The instantly claimed compounds (all stereoisomers) with R_1,R_2 = H are simply the

adjacent higher homologues with one additional chain methylene unit between the double bond and the amidino group. One of ordinary skill in the art would have had the expectation of similar properties for the instant compounds and those of Beams since they are adjacent homologues. The instantly claimed compounds are therefore *prima facie* obvious those of Beams.

Beams further teaches (Page 16, lines 15 – 25) methods for the selective inhibition of the inducible form of nitric oxide synthase over the constitutive form using the compounds of his invention. Because the instantly claimed compounds are *prima facie* obvious so are the methods for their use which are precisely coincident with that taught by Beams.

Thus the instantly claimed methods of use would have been obvious to one of ordinary skill in the art. The motivation for the instantly claimed invention would have been to develop other compounds in the genus taught by Beams and apply them, in the compositions taught by Beams, to the methods taught by Beams. The expectation for success would have been near certitude since Beams teaches that his compounds have the instantly desired activity as selective inducible nitric oxide synthase inhibitors.

Examiner's Response to Applicants' Remarks with Regard to This Rejection

Applicants have presented no arguments with regard to this rejection.

Claim Objections

7. Claims 4-7, 12-15 and 20-23 are finally objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Allowable Subject Matter

8. Claims 4-7, 12-15 and 20-23 are drawn to allowable subject matter. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art of record, Beams et al (WO 93/13055-A1 07-1993), does not provide sufficient guidance to allow one of ordinary skill in the art to select the instantly claimed methyl-substituted heptenoic acids from the genus taught. Because Beams exemplifies no alkyl-substituted compound of ordinary skill in the art would not have had a reasonable expectation of success in producing the instantly claimed methyl-substituted retinoic acids with the desired selectivity of ions inhibition.

Conclusion

9. Claims 1-32 are pending. Claims 1-3, 8-11, 16-19 and 24-32 are finally rejected. Claims 4-7, 12-15 and 20-23 are finally objected to.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker, Ph. D.
Patent Examiner
Technology Center 1600

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Technology Center 1600